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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TURNER, SHARON L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,191	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11-29-04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58-65,68-70 and 74-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-65,68-70 and 74-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

1. The amendment filed 11-29-04 has been entered into the record and has been fully considered.

2. The Examiner acknowledges receipt of a request under Rule 1.48(b) to delete the names of certain inventors. The request is in conformance and is therefore granted. The appropriate fee will be charged via Applicant's authorization.

3. The Examiner acknowledges receipt of a declaration under 37 CFR 1.131. However, the declaration has not been considered further as the declaration is unexecuted (not signed).

4. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

5. As a result of Applicants amendment, all rejections not reiterated herein have been withdrawn.

6. Claims 58-65, 68-70 and 74-77 are pending.

Priority

7. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), 120 and 365(c) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v.*

Performance Contracting, Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Applicant's have amended the first line of the specification as directed in the preliminary amendment submitted 8-4-03. The amendment identifies multiple US serial numbers, PCT international applications and provisional applications. Applicant's have also submitted a supplemental communication of 6-21-02 that provides a priority map and identifies particular applications in which PRO320 (SEQ ID NO's:118 and 119) is allegedly disclosed. The map notes that the first disclosure is within US provisional 60/078,004. These sequences are found in this priority application. However, utility is granted based upon activity in EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326. However, support for activity in this assay is not found in the priority applications until the filing of PCT/US99/05028, filed 3-8-99. As priority is not found until the 3-8-99 filing date, this application has been examined with the effective filing date of 3-8-99. Priority cannot be granted where no support for the activity of the noted sequences is provided.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page numbers of any parent application filed prior to 3-8-99 which specifically supports the claim limitations for each and every claim limitation in all the pending claims which Applicant considers to have been in possession of and fully enabled prior to 3-8-99.

Utility

8. Utility is established based upon EXAMPLE 109: Ability of PRO Polypeptides to

Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326 of the specification.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 58-62, and 74-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NO:118 which encodes SEQ ID NO:119 exemplified as exhibiting activity EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326, does not reasonably provide enablement for the variable polynucleotide and peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

The skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. For example, Jobling et al, Mol. Microbiol., 1991, 5(7):1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of conserved structural components to both biological function and immunological recognition.

Instant specification discloses a single PRO320 sequence that differs from the other sequences disclosed. The specification notes that the peptide exhibits activity in EXAMPLE 109: Ability of PRO Polypeptides to Inhibit Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth (Assav 9) at p. 326. However, the specification fails to note such conserved activities in any 80-99% variable molecule. However, applicants claims are directed to polynucldoetides encoding peptides with 80-99% homology, to extracellular domains, to sequences lacking the signal peptide and to hybridizing sequences where no requisite function is required.

The specification does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity. The specification provides essentially no guidance as to which of the essentially infinite possible choices is likely to be successful

and the skilled artisan would not necessarily expect functional conservation among homologous sequences. Moreover, no similar function is required of the additional sequences. The artisan would be unable to determine how to use such similar sequences that lack common function. The additional members would require further experimentation to discover their requisite use. Thus, applicants have not provided sufficient guidance to enable one skilled in the art to make and use the claimed derivatives in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Thus, in view of the quantity of experimentation necessary, the lack of working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims the artisan cannot make and use the invention without undue experimentation.

In the response of 11-29-04, Applicants argue that the amendments reciting that "the encoded polypeptide inhibits endothelial cell growth" is sufficient to enable the genus with respect to the breadth of 85-99% variability and assert that the artisan could make and use the claimed invention as supported via reference to MPEP 2164.01.

Applicants arguments filed 11-29-04 have been fully considered but are not persuasive. An analysis under In re Wands does not support that more likely than not

amino acids with as much as 85-99% variability would retain the noted function. The specification only demonstrates activity for the PRO320 sequence and as noted previously the prediction of function based upon structure is unpredictable in the art because single amino acid exchanges affect significantly protein structure folding and requisite activity. Such facts are notably exemplified in Skolnick and Jobiling as set forth above. Accordingly, the specification fails to support enablement for every single amino acid substitution along its length as encompassed by 99% homology languagej or for variations with up to 85% identity. The specification fails to teach which residues are important to functionality and fails to exemplify any 99% sequences that exhibit conserved function. Rejection is therefore maintained.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 58-65, 68-70 and 74-77 are rejected under 35 U.S.C. 102(e) as being anticipated by Ford et al., US Patent No. 6,392,018 filed 2-12-1999 and issued May 21, 2002.

Ford et al., teach EGF Motif protein obtained from fetal liver-spleen cDNA library, see in particular title, abstract. The protein is distinguished by Ford as SEQ ID NO:19

bearing 100% similarity to instant SEQ ID NO:119 encoded by SEQ ID NO:118. The signal sequence is taught at column 1, lines 18-39, column 5, lines 49-59, Figure 5, and column 9, lines 20-26. The extracellular portion is noted for example at column 6-7, paragraph spanning, column 9, lines 46-50, and column 10, lines 16-25 denoted by "soluble" portions as described at column 11, lines 5-12, having transmembrane and intracellular portions deleted, also signal sequences deleted or mature forms are noted at column 10, lines 16-25. Also discussed are hybridizing and variable sequences (80-99%) as noted at column 12, line 50-column 13, line 49. Ford further denotes vectors, host cells and suitable methods for expression, see in particular columns 13-21, for example. Thus, the reference teachings anticipate the claimed invention.1.

Applicants traverse rejection in the response of 11-29-04 via submission of a declaration under 37 CFR 1.131.

Applicants traversal is not persuasive because as noted above the declaration is un-executed. Therefore, rejection is maintained. Benefit of priority is 3-8-99 but the reference filing date is prior.

Conclusion

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached at (571) 272-0961.

SHARON L. TURNER, PH.D.
PATENT EXAMINER

Sharon L. Turner, Ph.D.
February 21, 2005